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**In Vivo Suppression of HIV by Antigen Specific T Cells Derived from Engineered Hematopoietic Stem Cells.**

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**Authors:** Scott G Kitchen, Bernard R Levin, Gregory Bristol, Valerie Rezek, Sohn Kim, Christian Aguilera-Sandoval, Arumugam Balamurugan, Otto O Yang, Jerome A Zack

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**Public Summary:**

**Scientific Abstract:**

The HIV-specific cytotoxic T lymphocyte (CTL) response is a critical component in controlling viral replication in vivo, but ultimately fails in its ability to eradicate the virus. Our intent in these studies is to develop ways to enhance and restore the HIV-specific CTL response to allow long-term viral suppression or viral clearance. In our approach, we sought to genetically manipulate human hematopoietic stem cells (HSCs) such that they differentiate into mature CTL that will kill HIV infected cells. To perform this, we molecularly cloned an HIV-specific T cell receptor (TCR) from CD8<sup>+</sup> T cells that specifically targets an epitope of the HIV-1 Gag protein. This TCR was then used to genetically transduce HSCs. These HSCs were then introduced into a humanized mouse containing human fetal liver, fetal thymus, and hematopoietic progenitor cells, and were allowed to differentiate into mature human CD8<sup>+</sup> CTL. We found human, HIV-specific CTL in multiple tissues in the mouse. Thus, genetic modification of human HSCs with a cloned TCR allows proper differentiation of the cells to occur in vivo, and these cells migrate to multiple anatomic sites, mimicking what is seen in humans. To determine if the presence of the transgenic, HIV-specific TCR has an effect on suppressing HIV replication, we infected with HIV-1 mice expressing the transgenic HIV-specific TCR and, separately, mice expressing a non-specific control TCR. We observed significant suppression of HIV replication in multiple organs in the mice expressing the HIV-specific TCR as compared to control, indicating that the presence of genetically modified HIV-specific CTL can form a functional antiviral response in vivo. These results strongly suggest that stem cell based gene therapy may be a feasible approach in the treatment of chronic viral infections and provide a foundation towards the development of this type of strategy.

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